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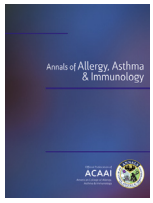

Perspectives

Ketotifen in the management of chronic urticaria: resurrection of an old drug

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Introduction

Ketotifen is an oral antiallergic drug developed in 1970 by Sandoz Pharmaceuticals of Switzerland. It is a benzocycloheptathiophene derivative and was initially marketed as an inhibitor of anaphylaxis.[1] The pharmacodynamic properties of ketotifen are many, because it is an inhibitor of the release and/or activity of mast cell and basophil mediators, including histamine, neutrophil, and eosinophil chemotactic factors, arachidonic acid metabolites, prostaglandins, and leukotrienes.[2] Thus, it inhibits the bronchial response to inhaled histamine, allergen, or aspirin. In addition, the ocular, nasal, and dermal responses to applied allergen in sensitized patients are attenuated with use of ketotifen.[3] It also has been found to have some calcium antagonist activity and to inhibit responses to platelet-activating factor from proinflammatory cells, such as eosinophils.[2] Additional possible modes of action include its ability to reverse β_2-agonist–induced decreases in β-adrenoreceptor density and to alter the affinity of these receptors and increase intracellular concentrations of cyclic adenosine monophosphate.[3] Ketotifen has a chemical structure similar to some first-generation antihistamines, such as cyproheptadine and azatidene.[2] With regard to the pharmacokinetic properties of ketotifen, it is readily absorbed from the gastrointestinal tract after oral administration and achieves peak plasma concentrations within 2 to 4 hours of administration. Clearance of the drug from plasma is biphasic, with a half-life of distribution of 3 hours and a half-life of elimination of 22 hours in adults.[3] However, the onset of action of ketotifen is slow, and it may take 4 to 6 weeks to achieve full prophylactic value under certain conditions.[4]

Ketotifen was originally patented by Sandoz in the 1970s. It became very popular for management of asthma in Japan and clinical trials were initiated in the United States in the 1980s for management of asthma and other allergic conditions. One author served on the Food and Drug Administration (FDA) Pulmonary–Allergy Drugs Advisory Committee and chaired that group from 1984 to 1986. Approval for treatment of asthma was not granted, but FDA staff did recommend more extensive evaluations for management of urticaria. Unfortunately, the latter studies have not been performed in a robust fashion. However, oral ketotifen has been used in patients with asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, chronic urticaria, cold-induced urticaria, cholinergic urticaria, exercise-induced urticaria, mastocytosis, and food allergy in Canada, Europe, and Mexico. Approval was granted for ocular administration in the United States for allergic conjunctivitis and later the drug became available over the counter. A review of clintrials.gov shows evaluations of ketotifen by oral administration for fibromyalgia, atopic dermatitis, attenuation of reactions during peanut desensitization, allergic rhinitis, asthma, and post-traumatic joint contractures. The authors became aware that ketotifen could be obtained in the United States from compounding pharmacies and began prescribing it more extensively in their clinics for severe urticaria in 2011. For adults and older children with asthma or allergic disease, the recommended dose of ketotifen is 1 mg twice daily. For young children 6 months to 3 years old, the recommended dose is 0.5 mg twice daily.[3]

It must be noted that oral ketotifen can be safely compounded in the United States. Pharmacy compounding is a practice in which a licensed pharmacist combines, mixes, or alters ingredients in response to a prescription to create a medication tailored to the medical needs of an individual patient. Pharmacy compounding, if performed properly, can serve an important public health need if a patient cannot be treated with an FDA-approved medication. The issue of safety of compounded drugs in the FDA Compliance Policy for Pharmacy Compounding is primarily for injectable drugs and does not relate to oral compounded drugs. This policy does include a select list of compounding drugs that were withdrawn or

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removed from the market for safety reasons, which does not include ketotifen.[5]

Oral ketotifen is usually well tolerated and relatively safe, with the most frequent side effect of sedation. This is seen in approximately 10% to 20% of patients, especially at higher doses, but the effect decreases within 1 to 2 weeks of use.[3] Other rarer reactions include dizziness, dry mouth, nausea, and headache, which have been reported in 1% to 2% of patients at initiation of therapy. However, these side effects do not persist in patients on long-term treatment. Weight gain and central nervous stimulation also have been reported in a small number of patients.[3,6] Ketotifen may potentiate the effects of central nervous system depressants, antihistamines, and alcohol. Concomitant use of oral ketotifen with oral diabetic agents, such as glyburide and metformin, may result in reversible thrombocytopenia.[7]

Most studies published on the use of ketotifen have focused on its benefits in childhood and adult asthma. However, by inhibiting the release of the proinflammatory mediators listed earlier, ketotifen can prevent the vascular permeability changes that are involved in the development of wheals and flare responses. Thus, it can be used in the management of urticaria. Several studies have been published evaluating the use of ketotifen for the management of urticarial syndromes, including cold-induced urticaria, heat-induced urticaria, exercise-induced urticaria, pressure-induced urticaria, cholinergic urticaria, and chronic idiopathic urticaria. However, overall, there is a paucity of literature on this topic, because ketotifen is not an FDA-approved drug in the United States for the management of urticaria (Table 1).[1,2,4,6,8–20]

Published Studies

Two early studies on the use of ketotifen in the management of urticaria were published in the early 1970s in Denmark. Ketotifen was compared with dimetinden and cyproheptadine in patients with chronic idiopathic urticaria. Results showed that ketotifen was superior to dimethindene and cyproheptadine because the patients showed significant improvement in pruritus, erythema, and number of papules. The investigators concluded that ketotifen was a safe and effective drug for patients with urticaria.[8,9]

Another early study, published in 1981, focused on patients with urticaria who were poorly responsive to antihistamines. Patients were treated with ketotifen and terbutaline because these 2 medications increase cellular cyclic adenosine monophosphate and inhibit mast cell degranulation. It was found that the combination of ketotifen and terbutaline was effective.[10]

Two studies from Spain, published in the early 1980s, evaluated chronic urticaria and treatment with ketotifen. These 2 studies concluded that ketotifen was effective and safe.[10,11] It also was concluded that ketotifen was an excellent therapeutic option in patients with urticaria and angioedema, especially in those cases in which traditional therapies have failed.[12]

An additional 2 articles, published in Germany in 1985, studied the effect of ketotifen in the management of urticaria. These articles concluded that ketotifen has a good suppressive effect on wheals and pruritus seen in chronic idiopathic urticaria, cholinergic urticaria, and urticaria factitia. The 2 studies noted that ketotifen had a good safety and tolerability profile.[13,14]

A placebo-controlled, double-blinded, crossover trial in Canada evaluating the effect of ketotifen treatment in cold-induced urticaria was published in 1985. The investigators concluded that ketotifen may have a place in the treatment of primary acquired cold urticaria even in patients known to be resistant to the effects of standard antihistamines, possibly because of its calcium antagonist and platelet-activating factor inhibitor effects.[2]

A study published in France in 1986 evaluated the effect of ketotifen on patients with various forms of chronic urticaria. Their

Table 1
Summary of all studies published evaluating ketotifen in the treatment of urticaria

Year published	Country published	Reference	Patients, n	Study type	Duration	Outcomes
1975	Denmark	Kuokkanen[8]	28	single-blinded comparative study: ketotifen vs dimethindene in chronic urticaria	4 wk	ketotifen > dimethindene
1977	Denmark	Kuokkanen[9]	50	randomized double-blinded study: ketotifen vs cyproheptadine in chronic urticaria	4 wk	ketotifen > cyproheptadine
1981	England	Saihan[10]	12	ketotifen + terbutaline vs ketotifen alone in CIU	8 wk	ketotifen + terbutaline > ketotifen alone
1982	Spain	Camarasa and Moragas[11]	36	ketotifen in different forms of urticaria		ketotifen is effective and safe
1984	Spain	Piñol and Carapeto[12]	26	ketotifen in CIU + angioedema		ketotifen is effective and safe
1985	Germany	Cap et al[14]	40	ketotifen in cholinergic urticaria and urticaria factitia		ketotifen is effective and safe
1985	Germany	Taube et al[13]	21	ketotifen in chronic urticaria	4 wk	ketotifen is effective
1985	Canada	St-Pierre et al[2]	11	double-blinded placebo-controlled crossover trial: ketotifen vs placebo in cold urticaria	3 wk	ketotifen > placebo
1986	France	Guillot and Meynadier[15]	36	ketotifen in chronic urticaria		inconclusive results; best results in cold and food-related urticaria
1986	Thailand	Phanuphak and Locharernkul[16]	30	double-blinded placebo-controlled trial: ketotifen vs placebo		ketotifen > placebo
1989	USA	Huston et al[17]	3	ketotifen in cold urticaria, exercise-induced urticaria, and dermatographism	4 wk	ketotifen effective
1989	Japan	Kamide et al[1]	305	double-blinded comparative study: ketotifen vs clemastine in CIU	2 wk	ketotifen > clemastine
1989	USA	McClean et al[18]	4	case report: ketotifen in cholinergic urticaria	9-mo to 2.5-y follow-up	ketotifen effective
1995	Thailand	Visitsunthorn et al[19]	6	double-blinded crossover trial: ketotifen vs cyproheptadine in cold-induced urticaria	10 wk	ketotifen = cyproheptadine, ketotifen with less side effects
1998	Turkey	Taşkapan and Harmanyeri[20]	18	blinded controlled trial: ketotifen vs cetirizine	4 wk	ketotifen = cetirizine
1997	USA	Egan and Rallis[6]	4	case report: ketotifen in CIU		ketotifen is effective and safe
1998	Sweden	Vena[21]	40	randomized double-blinded trial: ketotifen + nimesulide vs prednisone in delayed pressure urticaria	7 wk	ketotifen + nimesulide = prednisone
2002	Turkey	Karaayvaz et al[4]	60	ketotifen vs levothyroxine in chronic urticaria and thyroid autoimmunity	6 wk	levothyroxine > ketotifen

Abbreviation: CIU, Chronic idiopathic urticaria.

results were inconclusive, but it was noted that the best results were seen in patients with cold urticaria and food-related urticaria.[15]

During the 42nd annual meeting of the American Academy of Allergy, Asthma, and Immunology in 1986, an abstract presenting a double-blinded, placebo-controlled study evaluating ketotifen in the treatment of chronic urticaria was published. Results showed that symptoms significantly improved and the need for chlorpheniramine was significantly decreased in the group treated with ketotifen.[16]

The first article evaluating ketotifen for the treatment of urticaria in the United States was published in 1989. The objective of the study was to determine whether ketotifen could prevent cutaneous mast cell degranulation in vivo and thus produce clinical benefit in patients with physical urticarias. The study reported on 3 patients who were unresponsive to maximum tolerated doses of antihistamines or antiserotonin agents. Therapy was associated with marked inhibition of symptoms and histamine release. In addition, no adverse effects were seen during follow-up. It was concluded that although the mechanism by which ketotifen prevented clinical symptoms and inhibited histamine release is unclear, ketotifen can have therapeutic benefit in mast cell–mediated diseases.[17]

A large double-blinded study published in Japan compared the effect of ketotifen with that of clemastine, a commonly used antihistamine, in patients with chronic urticaria. It was found that ketotifen was more effective than clemastine because it showed a significant decrease in severity of wheals and pruritus and an increase in global improvement rating. Side effects observed in the ketotifen group were drowsiness, fatigue, diarrhea, and dizziness. It was concluded that ketotifen can effectively relieve pruritus and skin eruptions in patients with chronic urticaria.[1]

Another article published in the United States reported on patients with refractory cholinergic urticaria successfully treated with ketotifen. All 4 patients in this study had been treated previously with maximum doses of conventional antihistamine therapy and/or steroids without benefit. All patients were challenged with exercise, cold, or heat, depending on their triggers, before and during treatment with ketotifen. All patients showed symptomatic improvement during challenges while on ketotifen and experienced marked clinical improvement during follow-up. The investigators also noted that ketotifen blocks release of histamine, evidenced by decreased plasma histamine levels during challenges while patients were receiving the drug. Thus, in patients with cholinergic urticaria, ketotifen is more effective than other potent histamine receptor antagonists. As other researchers have noted, these investigators concluded that its mechanism appears to be a stabilizing action on mast cells.[18]

A double-blinded crossover trial with ketotifen and cyproheptadine (the first H_1 antihistamine that was known to be effective in the treatment of cold urticaria) was performed in Thai children with cold urticaria in 1995. The investigators concluded that ketotifen is as effective as cyproheptadine in treatment of cold urticaria with fewer side effects.[19]

A case report published in the United States in 1997 described the use of ketotifen in the management of urticaria. A 43-year-old woman with refractory chronic urticaria purchased ketotifen from Mexico, initiated treatment, and all other medicines for her urticaria were discontinued. Within days, her urticaria and pruritus resolved. The article also mentioned an additional 3 patients with chronic refractory urticaria who purchased ketotifen from Mexico and subsequently had marked improvement in their symptoms and less need for additional medications. Based on these observations, these investigators concluded that double-blinded research studies evaluating ketotifen for the treatment of chronic idiopathic urticaria must be performed.[5]

Of interest, a letter to the editor was published in the same journal after that article by 2 Turkish physicians. The physicians noted that ketotifen is widely used in Turkey for urticaria, atopic dermatitis, allergic rhinoconjunctivitis, and pediatric asthma and that ketotifen should be considered a first-line therapeutic agent in patients with chronic urticaria.[20]

Future Directions

Oral ketotifen has been widely used in Europe, Canada, and Mexico; however, a limited number of studies have been published regarding its use in the treatment of urticaria. Furthermore, oral ketotifen is not approved by the FDA for use in the United States. As mentioned earlier, there are several case reports and several small controlled studies evaluating the efficacy of ketotifen in the management of chronic urticaria. The current recommended stepwise approach to the treatment of urticaria considers immunosuppressive and/or immunomodulatory agents when symptoms are refractory to traditional therapies, such as antihistamines and leukotriene modifiers. Ketotifen has been shown to be beneficial and is a more cost–effective and safe additional therapy in the treatment of refractory chronic urticaria.

The allergy and immunology division at the authors' institution sought to evaluate whether treatment with oral ketotifen would provide symptomatic benefit in patients with refractory chronic idiopathic urticaria and idiopathic angioedema using a retrospective analysis. Institutional board review approval and informed consent were obtained from all patients. Twenty-four of 51 patients prescribed ketotifen in the past 2 years agreed to participate in the study. Patients were asked to complete a modified Urticaria Activity Score questionnaire to evaluate symptoms before and after starting ketotifen and document the use of additional medications. Medication use was scored by a point system, with higher points assigned to more potent medications. Urticaria Activity Scores improved in most patients (18 of 24) after starting ketotifen (Table 2). No patients thought that ketotifen made their symptoms worse, and 22 of 24 patients reported that ketotifen made their symptoms better. Sedation was the most frequent side effect reported. In addition, medication scores in 14 of 24 patients

Table 2
Retrospective analysis regarding use of ketotifen for treatment of chronic urticaria and angioedema: patient data

Patient	Age (y)	Sex	Race	AE	Thyroid	Auto	Δ UAS	Before UAS	After UAS
1	33	F	UNK	0	0	0	0	4	4
2	54	F	W	1	0	0	4	6	2
3	33	F	W	0	1	0	2	3	1
4	64	M	W	1	0	0	2	2	0
5	51	F	W	1	0	0	2	5	3
6	46	F	W	1	0	1	4	6	2
7	65	F	W	0	1	1	6	6	0
8	36	M	W	0	1	1	6	6	0
9	59	F	W	0	1	0	1	4	3
10	28	F	W	1	1	0	2	6	4
11	61	M	W	1	0	1	2	6	4
12	46	M	W	0	0	0	0	4	4
13	46	M	W	1	0	0	3	4	1
14	28	F	W	1	1	0	2	4	2
15	70	M	H	1	0	0	2	2	0
16	47	M	W	0	0	0	4	6	2
17	52	F	W	1	0	0	0	4	4
18	52	F	W	0	0	0	0	4	4
19	50	F	W	1	0	0	4	6	2
20	74	F	W	1	0	0	0	6	6
21	53	F	W	0	0	0	4	6	2
22	58	M	B	0	0	0	3	5	2
23	63	F	W	1	0	0	1	2	1
24	70	F	W	0	0	0	0	6	6

Abbreviations: AE, Angioedema; Auto, Autoimmune condition; B, black; Δ, change in; F, female; H, Hispanic; M, male; UAS, Urticaria Activity Score; UNK, unknown; W, white.

decreased, indicating the need for less medication after starting ketotifen. Most importantly, 4 of 6 patients were able to stop systemic steroids after starting ketotifen. The mean change in the Urticaria Activity Score after being on ketotifen was 2.25 (95% confidence interval 1.444–3.007, paired *t* test).

Based on these results, ketotifen may be used as a favorable addition to traditional medications in patients with refractory urticaria. The side effects of ketotifen are nominal and could minimize the need for other potentially harmful medications. This analysis adds to several case reports and small studies evaluating the efficacy of ketotifen in the management of chronic urticaria. The authors realize the power of this study is limited; however, a controlled prospective trial is planned to further the evidence that ketotifen has a beneficial effect in the treatment of chronic urticaria.

The use of oral ketotifen addresses a critical gap in drugs available to patients with antihistamine-resistant chronic idiopathic urticaria and all physicians in the United States can prescribe this medication.

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